

- 5 (3) The claim differs from Lee only in the recitation of homologous side groups. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute homologous side groups with the expectation of constructing a product having similar useful properties.

B. Analysis--Obviousness

(1) To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. MPEP 2143.03 and *In re Royka* 180 USPQ 580 (CCPA 1974).

- 10 None of the structures disclosed by Lee teach or suggest all of the limitations of the subject claims. The cited xanthene dye compound, CAS Registry No. 142975-78-8 corresponding to Figure 6, g. ddG-bifluor compound in Lee, p. 2478 does not contain the limitation of claim 1 of the present application where:

- 15 R_1 taken separately is selected from the group consisting of phenyl, substituted phenyl, polycyclic aromatic, substituted polycyclic aromatic, and electron-rich heterocycle, or when taken together with R_7 is selected from the group consisting of electron-rich heterocycle and indene;

20 page 39, lines 13-16

None of the structures disclosed by Lee bear the above groups at positions corresponding R_1 and R_7 positions. Thus Lee may not be held to render claim 1 of the present application obvious.

- 25 (2) Lee does not teach, disclose, or discuss phosphoramidate (+5 valence phosphorus) or phosphoramidite (+3 valence phosphorus) derivatives. Lee does not teach methods of sequencing and polynucleotide fragment analysis with R_1 and R_7 aromatic-substituted xanthene dyes of the present application.

- 30 (3a) To render a claim obvious, a proposed modification or combination must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen, Inc. v. Chugai Pharmaceutical Co.* 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Beyond looking at the prior art to determine if it suggests doing what the inventor has done, one must also consider if the art provides the required expectation of succeeding in that endeavor. "The consistent
35 criterion for determination of obviousness is whether the prior art would

have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in light of the prior art. Both the suggestion and the expectation of success must be founded on the prior art, not in the applicant's disclosure." (*In re Dow Chemical*, 5 USPQ2d 1529, 1531). Moreover, "The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification" *In re Gordon et al.*, 733 F.2d 900, 221 USPQ 1126 (Fed. Cir. 1984).

10 No reasonable expectation of success existed at the time of the present invention that the aromatic-substituted xanthene dyes of the present invention would possess particularly advantageous spectral properties. It is well known in the art that minor structural modifications in fluorescent, xanthene dyes engender significant changes to their physical and chemical properties. As
15 evidenced by a large body of literature, the correlation between fluorescent dye structure and their spectral properties is not well understood.

Spectral properties of aromatic-substituted xanthene dyes and nucleic acid fragments labelled with them are the primary utility of the present invention. Applicant has demonstrated that when the R₁ and R₇ positions are substituted
20 with aromatic groups the important and practical advantages of narrow fluorescent bands (reduced width of emission spectra) and high levels of brightness (extinction coefficient and quantum yield) are conferred relative to structurally similar fluorescent dyes, particularly those lacking the aromatic substitution moiety, see p. 37, Table 1.

25 Furthermore, the relationship between molecular structure and spectral properties in fluorescent dyes is complex and unpredictable. Optimum performance, as evidenced by the R₁ and R₇ aromatic-substituted xanthene dyes, requires extensive experimentation, cannot be predicted, and must be determined empirically. Tangible evidence of unpredictability and a lack of a
30 reasonable expectation of success is the hundreds of related fluorescent dye analogs with homologous side groups that do not give similar useful results or have useful spectral properties. The R₁ and R₇ aromatic-substituted xanthene dyes gave unexpected and advantageous properties of increased brightness, emission maxima shifting to longer wavelengths, and enzymatic incorporation
35 when labelled on nucleotides, relative to xanthene dyes where R₁ and R₇ are hydrogen or chloro (HEX). These improvements translate to larger peaks and improved DNA sequencing and fragment analysis results. Furthermore, the advantages and improvements are not correlated by chemical structural

similarity, i.e., the R₁ and R₇ aromatic-substitution pattern shows an unexpected and superior result.

(3b) "References relied upon to support a rejection for obviousness must provide an enabling disclosure. That is to say, they must place the claimed invention in the possession of the public." *Beckman Instruments, Inc. v. LKB Produkter AB*, 13 USPQ2d 1301 (Fed. Cir. 1989). In the case of an invention directed to a chemical compound:

[I]f the prior art of record fails to disclose or render obvious a method for making a claimed compound...it may not be legally concluded that the compound itself is in the possession of the public. In this context, we say that the absence of a known or obvious process for making the claimed compounds overcomes a presumption that the compounds are obvious, based on close relationships between their structures and those of prior art compounds.

In re Hoeksema, 158 USPQ 596 (1968)

Lee does not teach how to make the R₁ and R₇ aromatic-substituted xanthene compounds. Lee teaches only the synthesis of one dye, lacking substituents at R₁ and R₇ ("EVE", p. 2473). The present application includes extensive examples of the synthesis of R₁ and R₇ aromatic-substituted xanthene compounds (Examples 1-17, p. 30-36). The invention of the present application required: (i) the non-obvious and particular substituents and substitution pattern among the many million possible analogs, (ii) methods for their synthesis, and (iii) methods and conditions for their use.

The Lee reference is not sufficiently enabled to support a rejection under 35 USC § 103(a) because it does not render obvious the aromatic-substituted xanthene compounds of the present invention to one of ordinary skill in the chemical arts. Accordingly, the present rejection should be withdrawn.

III. CONCLUSION

In view of the foregoing amendments and remarks, the Applicants submit that the claims pending in the present application are in condition for allowance. A Notice of Allowance is therefore respectfully requested.

If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned at 650 638-5846.

IV. CONDITIONAL PETITION FOR TIME EXTENSION and FEE AUTHORIZATION

5 If any additional time extensions are required, such time extensions are hereby requested. If any additional fees not submitted with this response are required, please take such fees from deposit account number **01-2213**.

Respectfully submitted,

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